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IgM Anti-Hepatitis C Virus Core Antibodies as Marker of Recurrent Hepatitis C After Liver Transplantation

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The differential diagnosis of recurrent hepatitis C following orthotopic liver transplantation (OLT) may be difficult. We evaluated the diagnostic significance of IgM anti-hepatitis C virus (anti-HCV) core antibodies in 27 patients undergoing OLT because of HCV-associated cirrhosis. Serial serum samples collected before and after OLT were tested for the presence of IgM anti-HCV core antibodies. Results were compared with the histological evidence of liver damage, the presence, level, and genotype of serum HCV RNA and the degree of immunosuppression. All patients underwent recurrent HCV infection. Recurrent hepatitis was diagnosed histologically in 21 patients an average of 48 weeks after OLT (range 2–209 weeks): 18 had persistence or (re-)appearance of the IgM anti-HCV core after OLT, one lost the IgM anti-HCV core after OLT, and two never secreted IgM anti-HCV core either before or after OLT. The remaining six patients did not develop recurrent hepatitis after a follow-up of 44–241 weeks from OLT; in these patients, IgM anti-HCV core either disappeared (1 case) or decreased (1 case) after OLT or were persistently negative throughout the study (4 cases). Thus, 18/21 patients with recurrent hepatitis, but only one of six without recurrent hepatitis, secreted IgM anti-HCV core after OLT ($P < 0.05$). The IgM anti-HCV core levels were not correlated with the level or genotype of serum HCV RNA or the degree of immunosuppression. In conclusion, secretion of IgM anti-HCV core antibodies after OLT seems associated with recurrence of HCV-associated liver disease and may have diagnostic significance. ***J. Med. Virol. 56:224–229, 1998.***

KEY WORDS: anti-HCV IgM; hepatitis C virus; chronic hepatitis C; orthotopic liver transplantation; immunopathogenesis

INTRODUCTION

Almost all patients undergoing orthotopic liver transplantation (OLT) for hepatitis C virus (HCV)-related cirrhosis have recurrent HCV infection [Araya et al., 1997]. Conversely, recurrent hepatitis C is not universally seen, and one year after OLT up to 50% of patients may not have histological signs of recurrent liver disease due to HCV, in spite of high-level HCV viremia [Shah et al., 1992; Chazouillieres et al., 1994; Freeman et al., 1996; Zhou et al., 1996]. Therefore, in a clinical setting where the liver injury is multifactorial, the differential diagnosis of recurrent hepatitis C may be difficult.

The histological features of recurrent hepatitis C after OLT have been described in detail [Ferrell et al., 1992]. However, a significant proportion of liver biopsies may show atypical findings and the diagnosis may remain uncertain in as many as one third of cases [Ferrell et al., 1992]. The HCV RNA serum levels, the HCV genotype, and the amount of HCV antigens stained by immunohistochemistry have all been used as adjunct in the diagnosis of the acute recurrent hepatitis C post-OLT, but results are not unequivocal [Féray et al., 1995; Gretch et al., 1995; Vargas et al., 1995; Gane et al., 1996; Zhou et al., 1996; Negro et al., 1998].

In analogy with other viral infections [Farci et al.,

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1986; Govindarajan et al., 1989; Brunetto et al., 1993; Colloredo Mels et al., 1994], and in keeping with previous data on the clinical significance of IgM antibodies to the HCV core in chronic hepatitis C [Negro et al., 1995] and in transplanted patients [Negro et al., 1996a; Crespo et al., 1997], we examined the post-OLT kinetics of IgM anti-HCV core in a series of HCV RNA-positive cirrhotic patients undergoing OLT and compared the results with the presence of hepatitis at histology; the presence, level, and genotype of serum HCV RNA; and the degree of immunosuppression.

MATERIALS AND METHODS

Patients

Between April 1989 and December 1996, 32 patients with HCV-related, end-stage cirrhosis underwent an orthotopic liver transplantation at the Division of Digestive Surgery, University Hospital, Geneva (Switzerland). Five patients were not considered in the present study because of early (<1 month) death after OLT (3 cases) or concomitant hepatitis B virus (HBV) infection (2 cases). Among the remaining 27 patients, there were 18 males and 9 females; the mean age at liver transplantation was 50.1 years (range 31–63) (see Table I). After OLT, all patients received standard triple immunosuppression (STI), consisting in prednisone 100 mg on the first day post-OLT, tapered to 20 mg daily on day 10 and maintained for 6–12 months, plus azathioprine 1–2.5 mg/Kg daily, as well as cyclosporine A 2 mg/Kg intravenously daily followed by 5–10 mg/Kg per os daily. Individual variations to the STI are reported in Table I. The average post-OLT follow-up was 125 weeks (range 6–289 weeks) (Table I).

Serum Assays

Serum samples were collected every other week during the first 2 months and every month afterwards and stored at −80°C until use. Assays were carried out on selected samples and included assessment of the alanine aminotransferase (ALAT) activity, detection of antibodies to HCV structural and nonstructural proteins (by a second-generation ELISA (Ortho Diagnostics, Raritan, NJ), and HCV RNA by either a qualitative [Bukh et al., 1992] or a quantitative reverse transcription-polymerase chain reaction (RT-PCR)-based assay (Amplicor Monitor HCV, Hoffmann-La Roche, Basel, Switzerland). HCV genotyping was undertaken by a line probe assay (INNO-LiPA, Innogenetics, Antwerp, Belgium).

IgM antibodies to the HCV core protein were detected by a commercially available enzyme immunoassay (HCV-IgM EIA 2.0, Abbott GmbH Diagnostika, Wiesbaden, Germany), based on a recombinant HCV core protein (amino acids 1–150) expressed in *Escherichia coli* and adsorbed onto polystyrene beads to capture anti-HCV core antibodies of the IgM class, which are then detected by horseradish-conjugated goat antiserum to human IgM antibodies (μ-specific). Samples with a sample to cutoff (S/CO) ratio greater than or equal to 1.0 are considered positive. The specificity of this assay and the lack of interference due to rheumatoid factors have been described elsewhere [Pawlotsky et al., 1995; Negro et al., 1996b].

Liver Histology

Liver biopsy specimens were taken for histological evaluation from all patients on occasion of every ALAT elevation or, on a systematic basis, once a year in case of normal ALAT. Liver specimens were formalin-fixed, paraffin-embedded, and stained with hematoxylin-eosin and Masson's trichrome stainings. Histological diagnoses followed internationally accepted criteria [Martin et al., 1991; Gupta et al., 1995]. The histological grading and staging were scored as reported [Desmet et al., 1994].

Statistical Analysis

Differences among groups were evaluated by the Mann-Whitney's U test. Differences among proportions were evaluated by Fisher's exact test. Correlations were analyzed by the coefficient of correlation (continuous variables) or by the Spearman's rank correlation test (nonparametric data).

RESULTS

Recurrent HCV Infection and Histological Outcome

All 27 patients underwent recurrent HCV infection, as shown by detection of HCV RNA in serum by qualitative RT-PCR. In all 21 patients in whom a serum sample was available for testing, HCV RNA was already detectable by RT-PCR within two weeks after OLT.

Histological signs consistent with a diagnosis of recurrent hepatitis were observed in 21 patients an average of 48 weeks after OLT (range 2–209 weeks); in 18 patients the hepatitis progressed to chronicity, whereas in three patients, subsequent liver biopsies showed only minimal changes (Table I).

Six patients did not develop recurrent hepatitis, despite an average follow-up of 122 weeks (range 44–241 weeks), comparable to that of patients of the former group (P = NS). Two of these patients had an initial episode of acute rejection controlled by treatment, two had persistently normal liver tests and minimal changes at histology, and two developed a chronic rejection.

IgM Anti-HCV Core in Patients With Recurrent Hepatitis

Among the 21 patients with a histological diagnosis of post-OLT recurrent hepatitis, 17 were IgM anti-HCV core-positive before OLT, whereas four were IgM anti-HCV core-negative. After OLT, IgM anti-HCV core antibodies persisted in all patients who had tested positive before OLT except in patient 11, who lost these antibodies despite a definite diagnosis of recurrent hepatitis 29 weeks after OLT. IgM anti-HCV appeared ex novo in two patients who had tested negative before OLT.

TABLE I. Clinical and Histological Features of 27 Patients Undergoing OLT for HCV-Associated Cirrhosis and IgM Anti-HCV Core Antibodies[a]

At OLT					After OLT		IgM anti-HCV core	
Patient	Age	Sex	Genotype	Follow-up (weeks)	Histological outcome	Immunosuppression	Before OLT	After OLT
1	58	f	1b	78	hepatitis on week 30, followed by mixed features of hepatitis and rejection on week 78	STI	–	+
2	47	m	1b	273	nonspecific, MC throughout follow-up, then hepatitis on week 211	STI + 1 × 1 steroid bolus	+	+
3	55	m	2a/2c	6	rejection/hepatitis on week 2	STI + 4 × 1 steroid boluses; switched to TACRO on week 2	+	+
4	47	f	4	132	rejection on week 2, ischemia on week 4, then hepatitis on week 86	STI + 4 × 1 steroid boluses; added OKT3 on week 4	+	+
5	52	m	1b	59	MC on week 10, then hepatitis on week 59	STI	+	+
6	64	m	1b	126	rejection on week 2, acute cholangitis on week 9, then hepatitis on week 50	STI + 1 g steroid bolus	+	+
7	56	f	1b	12	hepatitis on week 7	STI	+	+
8	48	m	1b	148	rejection on week 9, then MC throughout follow-up, followed by hepatitis on week 149	STI	+	+
9	57	m	1b	205	rejection/hepatitis on week 3	STI + 600 mg steroid bolus	+	+
10	61	m	1b	19	toxic hepatitis on week 5, then rejection on week 7, then hepatitis on week 9	STI	–	–
11	38	f	3a	33	rejection on week 1, then massive steatosis throughout follow-up, then hepatitis on week 29	STI + 5 × 1 g steroid boluses; added OKT3 on week 2; added Atgam on week 3; switched to TACRO on week 3	+	–
12	56	f	1a/1b	288	rejection on week 4, then hepatitis on week 7	STI	+	+
13	43	m	4c/4d	202	rejection/hepatitis on week 13	STI; switched to TACRO on week 4	+	+
14	43	f	1b	9	rejection/hepatitis on week 2	STI + 2 × 1 g steroid boluses	+	+
15	41	m	3a	17	rejection/hepatitis on week 4	STI	+	+
16	53	m	1b	193	rejection on week 2, then MC throughout follow-up, hepatitis on week 118, then MC	STI + 3 × 1 steroid boluses	+	+
17	57	m	3a	288	rejection on week 20, then MC throughout follow-up, hepatitis on week 197, then MC	STI	–	–
18	58	f	1b	95	rejection on week 2, then hepatitis on week 3, then MC	STI + 3 × 1 g steroid boluses	–	–
19	37	m	NA	289	acute cholangitis on week 2, then hepatitis on week 50	STI	+	+
20	50	f	NA	115	hepatitis on week 30	STI	+	+
21	53	f	1b	61	hepatitis on week 12	STI	+	+
22	36	m	3a	73	MC throughout follow-up	STI	–	–
23	51	m	1b	68	MC throughout follow-up	STI	+	+
24	62	m	1b	44	rejection on week 8, then normal liver tests	STI	–	–
25	50	m	1b	198	rejection on week 2, then MC	STI	+	–
36	31	m	1a	241	chronic rejection	STI + 4 × 1 steroid boluses; switched to TACRO on week 70	–	–
27	50	m	1b	110	chronic rejection	STI + 3 × g steroid boluses; switched to TACRO on week 9	–	–

[a]f denotes female; m, male; NA, not assigned; OLT, orthotopic liver transplantation; MC, minimal changes; STI, standard triple immunosuppression; OKT3, murine antihuman thymocyte antiserum; Atgam, equine antihuman thymocyte antiserum; TACRO, tacrolimus.

In 13 patients, the S/CO value of IgM anti-HCV core tended to fall soon after OLT, reaching a value below the threshold for positivity in 8, to increase again thereafter. At the time of the nadir of the S/CO value, six patients experienced a liver enzyme elevation, which was histologically diagnosed as distinct from recurrent hepatitis and consisted in ischemia followed by acute rejection (patient 4), acute rejection alone (patients 8 and 16) (Fig. 1A and B, respectively), toxic hepatitis (patient 10) (Fig. 1C), or acute cholangitis (patients 6 and 19).

IgM anti-HCV could be detected before or at the same time as the first histological diagnosis of recurrent hepatitis in 12 patients. Secretion of IgM anti-HCV core preceded hepatitis sometimes by several months and occasionally by 209 weeks (patient 2). In the other five patients in whom this information could be reliably obtained, IgM anti-HCV core antibodies appeared in serum an average of six weeks after the hepatitis had recurred. At the end of follow-up, IgM anti-HCV core S/CO values were comparable or higher than before OLT in 15 patients, while they were lower in the other four.

Finally, two patients of this group were persistently IgM anti-HCV core-negative before and after OLT throughout the whole follow-up.

In conclusion, 18 out of 21 patients with recurrent hepatitis C after OLT secreted IgM anti-HCV core, compared to 1 out of 6 patients without histological evidence of recurrent hepatitis. This difference was statistically significant ($P < 0.05$).

IgM Anti-HCV Core in Patients Without Recurrent Hepatitis

Among the six patients who never developed recurrent hepatitis, four never secreted IgM anti-HCV core throughout the follow-up, one was IgM anti-HCV core-positive before OLT but became negative thereafter, and one had the S/CO level of the IgM anti-HCV core decreasing by 30% after OLT.

IgM Anti-HCV Core and ALAT Activity, Histological Grading and Staging, and Immunosuppressive Treatment

The IgM anti-HCV core level was not correlated with the ALAT activity level ($r = -0.15$), nor with the portal/periportal ($r = -0.0007$) or the lobular ($r = 0.27$) necroinflammation score or with the fibrosis score ($r = -0.017$).

IgM secretion did not appear to be influenced by the immunosuppression treatment, as exemplified by patient 10, who was IgM anti-HCV core-positive eight weeks after OLT at the time his recurrent hepatitis C was diagnosed and when he was receiving prednisolone, azathioprine, tacrolimus, and OKT3 antithymocyte antiserum because of rejection resistant to STI (Table I).

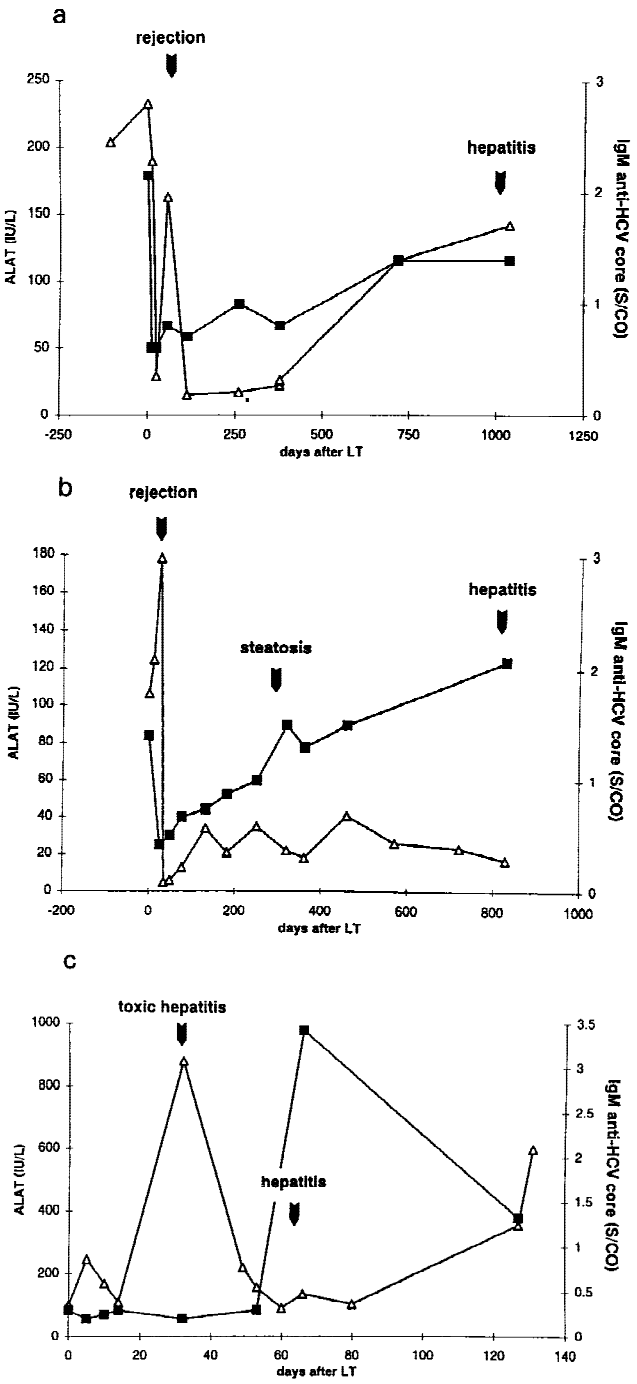

Fig. 1. Time course of serum ALAT activity (expressed as IU/L) (△——△) and IgM anti-HCV core antibodies (expressed as S/CO ratio) (■——■) after liver transplantation (LT) in patients 8 (**a**), 16 (**b**), and 10 (**c**).

IgM Anti-HCV Core and Level and Genotype of Serum HCV RNA

In 49 selected serum samples from 23 patients in which the quantitative RT-PCR for HCV RNA was carried out, no correlation was found between the S/CO values of the IgM anti-HCV core and the viremia levels ($r = 0.019$).

HCV genotype could be assigned in 25 patients: it was 1b in 17 patients (68%), 3a in three (12%), 1a in four, and a mixture of 1a/1b, 2a/2c, or 4c/4d in one each of the remaining five patients (Table I). The genotype of the six patients who were consistently IgM anti-HCV core-negative was 1b in three cases, 3a in two, and 1a in the last one.

DISCUSSION

We assessed the diagnostic significance of IgM anti-HCV core antibodies in patients with HCV-related cirrhosis undergoing OLT. The post-OLT pattern of IgM anti-HCV core antibodies seemed to be associated with the clinical and histological outcome. In a small proportion of cases (22% in our series), IgM anti-HCV core antibodies were persistently undetectable (i.e., before and after OLT), more often among patients who did not develop recurrent hepatitis (4 out of 6) than among those who did (2 out of 21). The persistent lack of detection of IgM anti-HCV has been reported in all previous series of patients, independently of the immunosuppression [Caporaso et al., 1994; Nagayama et al., 1994; Quiroga et al., 1995; Martinelli et al., 1996].

The persistence of IgM anti-HCV core antibodies after OLT, at levels comparable or higher than those observed before transplantation, was associated or followed by the development of recurrent hepatitis C in the grafted liver. The diagnostic significance of IgM anti-HCV core was also underscored in those patients in whom the liver damage occurring early after OLT was not due to HCV (acute cholangitis, ischemia, rejection), on which occasion the IgM anti-HCV core S/CO value often dropped to undetectable levels. There was no correlation with the degree of immunosuppression (expressed as the number of steroid boluses or the switch to more aggressive drugs, such as tacrolimus, OKT3 or Atgam, in order to control graft rejection). In fact, IgM anti-HCV core antibodies were also secreted in heavily immunosuppressed patients.

On the other hand, IgM anti-HCV core antibodies either were persistently undetectable or decreased or disappeared after OLT in all patients who did not develop recurrent hepatitis, and this despite recurrent HCV infection and throughout a follow-up comparable to that of patients with a definite diagnosis of recurrent hepatitis. In only one patient did IgM anti-HCV core antibodies persist after OLT, albeit the S/CO value decreased by 30% with respect to the pre-OLT level. Since the detection of IgM anti-HCV core may precede by several months the recurrence of the hepatitis, we cannot exclude that this patient may eventually develop a hepatitis later on during the follow-up.

Thus, the kinetics of IgM anti-HCV core may be a useful diagnostic adjunct even in the immunosuppressed patient. This seems particularly relevant in a clinical context where the establishment of a causal relationship between viral infection and liver damage is important for a proper management. The differential diagnosis of recurrent hepatitis C after OLT may be difficult, since both histological [Ferrell et al., 1992] and virological findings [Shah et al., 1992; Chazouillieres et al., 1994; Féray et al., 1995; Gretch et al., 1995; Pageaux et al., 1995; Vargas et al., 1995; Freeman et al., 1996; Gane et al., 1996; Negro et al., 1996a; Zhou et al., 1996] may fall short of providing a definite diagnosis. In fact, serum HCV RNA levels before OLT are not associated with a higher rate of recurrent disease or its earlier occurrence [Pageaux et al., 1995]. The infection with the viral genotype 1b may be associated with the development of recurrent hepatitis C, but some patients infected by type 1b may fail to undergo recurrent hepatitis, as shown by our present data, as well as by other reports [Féray et al., 1995; Gretch et al., 1995; Zhou et al., 1996]. The HCV viremia levels after OLT have been correlated with the acute recurrent hepatitis C [Gretch et al., 1995; Gane et al., 1996]. However, high levels of viremia can be found also in patients who do not develop histological evidence of hepatitis [Shah et al., 1992; Chazouillieres et al., 1994; Negro et al., 1998]. The discrepancy between presence and activity of liver disease, on the one hand, and levels of viral replication, on the other, was paralleled by the lack of correlation between the IgM anti-HCV core S/CO values and the serum HCV RNA levels shown in the present study, suggesting that immunological factors, rather than virological ones, are involved in the recurrence of HCV-associated liver disease after OLT.

In a parallel study [Negro et al., 1998], we reported that some patients may have after OLT very high levels of intrahepatic replication in the absence of recurrent hepatitis at histology. If the liver after OLT can tolerate high levels of HCV replication without developing a hepatitis, and if histological features suggestive of a direct cytopathogenicity of HCV are rare, then the pathogenesis of recurrent hepatitis C after OLT is likely to be immunomediated. High levels of HCV replication have been described irrespectively of the histological liver disease activity also in chronic hepatitis C patients [Shakil et al., 1995; Shindo et al., 1995; McGuinness et al., 1996], and the role of the host immune system in the pathogenesis of hepatitis C has been reaffirmed by recent reviews [Gonzalez-Peralta et al., 1994; Battegay, 1996].

In conclusion, the present data suggest that the host immune system may play a major role in determining occurrence, severity, and progression of recurrent hepatitis C after OLT, and that its diagnosis should therefore rely on immunological markers. In this respect, we suggest that the IgM anti-HCV core antibodies be used as indirect marker of recurrent, HCV-associated liver disease after OLT.

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